Effects of reserpine on the plasma half-time of [^{131}I]thyroxine

SIR,—Canary, Schaaf & others (1957), using reserpine, relieved the signs and symptoms of patients with thyrotoxicosis without influencing thyroidal [^{131}I]-uptake or the serum protein-bound iodine level. Although conflicting studies have been reported, reserpine probably has no direct effect upon thyroid-stimulating hormone (TSH) release, or the thyroidal metabolism of iodine (Watts, 1967). These reports led to the consideration that reserpine might have a direct peripheral anti-thyroxine effect.

Male Sprague-Dawley rats weighing 165–175 g were placed on a low iodine diet and divided into three groups. The animals in group A received 100 μg/kg of reserpine intraperitoneally daily for three days. They were then given 0·1 μg [^{131}I]thyroxine, initially containing 20·7 μc/μg, intraperitoneally. The same dose of resperpine was continued until the animals were killed. Group B received a single injection of 2 mg reserpine intraperitoneally 2 hr before receiving the [^{131}I]thyroxine. These doses of reserpine did not influence food intake. Group C received only the [^{131}I]thyroxine. Heparinized blood samples were taken from the tail at 6, 24, 48 and 72 hr after [^{131}I]thyroxine injection, and at 96 hr by direct cardiac puncture.

The plasma was subjected to paper chromatography (Taurog, Tong & Chaikoff, 1950), and the radioactivity of the thyroxine band was determined in a scintillation well-counter. By plotting these values (in counts/ml plasma) on semi-logarithmic paper and extrapolating back to zero time, the half-time of the plasma [^{131}I] thyroxine was obtained. At the time of death, the brain was removed and its 5-hydroxytryptamine (5-HT) content determined (Mead & Finger, 1961).

The control animals (Group C) yielded a plasma thyroxine half-time of 23 $\pm$ 0·3 hr, whereas the half-times in the acute (Group B) and the chronic (Group A) reserpine experiments were 23 $\pm$ 0·7 and 23 $\pm$ 1·0 hr respectively. The average brain 5-HT content from Group A was 0·33 $\pm$ 0·02 μg/g brain. One animal taken at random from Group C yielded a brain 5-HT content of 0·45 μg/g whereas one taken at random from Group B had a brain 5-HT content of 0·26 μg/g.

Reserpine did not seem to alter the plasma half-time of [^{131}I]thyroxine in doses which significantly lowered brain 5-HT content ($P < 0{\cdot}01$). Preliminary studies had demonstrated that the technique used for measuring thyroxine half-time was sufficiently sensitive enough to reveal a shortening of the half-time in unshorn rats at 4° by 25% and in rats given TSH by almost 50%.

Brodie, Davies & others (1966) reported that thyroid hormone increased the amounts of adenyl cyclase in adipose tissue. Catecholamines, by activating adenyl cyclase, increase the steady-state level of adenosine-3′,5′-phosphate which may be the chemical trigger mediating catecholamine action in sympathetic target organs (Sutherland & Rall, 1960). Therefore, since reserpine depletes catecholamines peripherally (Brodie, Olin & others, 1957), it may indirectly inhibit thyroid hormone function peripherally, without affecting its degradation, by reducing the availability of catecholamines, and thus limiting the activation of adenyl cyclase. This may explain why Canary & others (1957) noted relief of the signs and symptoms of patients with thyrotoxicosis who were treated with reserpine without noting any change in thyroidal [^{131}I]-uptake or in the serum protein-bound iodine level. Reserpine might be a useful agent in further studies of possible functional relations between peripheral thyroid hormone and catecholamines.

Department of Surgery,
Division of Neurosurgery,
The University of Texas,
Southwestern Medical School,
Dallas, Texas, U.S.A.

CLARK C. WATTS

March 15, 1968

References

Brodie, B. B., Davies, J. I., Hynie, S., Krishna, G. & Weiss, B. (1966). *Pharmac. Rev.*, **18**, 273–289.
Brodie, B. B., Olin, J. S., Kuntzman, R. G. & Shore, P. A. (1957). *Science, N.Y.*, **125**, 1293–1294.
Canary, J. J., Schaaf, M., Duffy, B. J. & Kyle, L. H. (1957). *New Engl. J. Med.*, **257**, 435–439.
Mead, J. A. R. & Finger, K. F. (1961). *Biochem. Pharmac.*, **6**, 52–53.
Sutherland, E. W. & Rall, T. W. (1960). *Pharmac. Rev.*, **12**, 265–299.
Taurog, A., Tong, W. & Chaikoff, I. L. (1950). *J. biol. Chem.*, **184**, 83–104.
Watts, C. C. (1967). Masters Thesis (Pharmacology). University of Texas, Dallas, Texas, U.S.A.

Effect of HC-3 on choline uptake by the isolated diaphragm

SIR,—It is generally accepted that the action of HC-3 reaches a maximum only at stimulation rates of 1/sec or more (Wilson & Long, 1959). This is believed to result from impairment of acetylcholine synthesis which becomes more important at higher frequencies of stimulation leading to depletion of transmitter stores. However, choline does not antagonize HC-3 blockade in the rat phrenic nerve-diaphragm preparation (Thies & Brooks, 1961), and the addition of choline to fluid bathing the diaphragm fails to increase acetylcholine output (Straughan, 1960). Thus, the supply of choline may not be a limiting factor in acetylcholine synthesis in the diaphragm as in the superior sympathetic ganglion (MacIntosh, 1963). While investigating [^{14}C]choline uptake in rabbit isolated, perfused hearts, it was of interest to examine [^{14}C]choline uptake by the rabbit diaphragm and the influence of HC-3 thereon.

The preparation consisted of the rabbit isolated, perfused phrenic nerve-diaphragm as first described by Burgen, Dickens & Zatwas (1949) and later modified for continuous perfusion by Dr. L. P. McCarty (personal communication). The diaphragms were perfused with a re-cycling system via the vena cava with oxygenated, eserinized Locke-Ringer solution, 37°, 5 ml/min, while suspended in a Locke-Ringer bath. Both phrenic nerves were placed over platinum electrodes and monophasic pulses of 0·5 msec duration and 5 V were delivered from a Grass 54B stimulator. The frequencies of stimulation ranged from 6/min to 10/sec and were administered for 5 min followed by 5 min rest. This intermittent stimulation was continued for 1 hr. The concentration of [^{14}C]choline in the perfusion fluid was 0·012 μg/ml. Extraction of [^{14}C]-labelled compounds and their subsequent paper chromatography are as previously described (Buterbaugh & Spratt, 1968).

The results obtained are shown in Fig. 1. The response to nerve stimulation was maintained throughout the 1 hr perfusion period at frequencies of 6/min and 1/sec. At 10/sec, the contraction response was vigorous at the start of each 5 min period and diminished to about 25% of the initial response by the end of each period. Higher stimulation frequencies resulted in tetany and were not used. It is evident that the highest uptake of [^{14}C]choline occurred at the lowest stimulation frequency, 6/min, and decreased to the lowest value at 10/sec.